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Later sibling Recurrence of ASD and ADHD: Clinical and Mechanistic Insights

Tony Charman[1*] PhD & Emily J. H. Jones[2] PhD

[1] Department of Psychology, Institute of Psychiatry, Psychology & Neuroscience, King's College London, UK.

[2] Centre for Brain and Cognitive Development, Birkbeck College, University of London, UK.

* Correspondence to: tony.charman@kcl.ac.uk

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Miller and colleagues[1] report on the within- and cross-condition recurrence of later born siblings of children ('probands') with attention deficit/hyperactivity disorder (ADHD) or autism spectrum disorder (ASD). The relatively high heritability of both conditions is well established from twin studies assessing both trait variance[2] and diagnostic recurrence[3]. Two recent large-scale Scandinavian studies extended this work to show that the two conditions also run together in families. One population-based study of children with ASD (*n*=3,578) estimated the combined (older and younger) sibling recurrence of ASD to be 10.5% but also reported that 5.3% had siblings with a diagnosis of ADHD, giving relative risks of 11.8 and 3.7 compared to matched controls without ASD[4]. An even larger population registry study with *n*=28,468 cases of ASD found that full siblings had a similarly elevated odds ratio of 4.59 of having an ADHD diagnosis compared to siblings of individuals without an ASD diagnosis[5]. This familial cross-aggregation between the two conditions highlights the importance both of providing clinically useful estimates of elevated likely recurrence rates and of studying shared neurodevelopmental paths to the two conditions[6].

Although the US medical records data reported by Miller et al[1] is more modest in scale than these large Scandinavian population studies it does speak very directly to a question of clinical concern. When parents are told by clinicians that their child has a diagnosis of a neurodevelopmental condition such as ASD or ADHD, one important question – often asked by parents themselves – is "What are the chances that my younger/future children will have ASD or ADHD?". To answer this question, we need to know the recurrence rates for *later* born siblings; the question directly addressed in the current study. Miller and colleagues[1] report that 12.03% of later born siblings of older probands with ASD also went on to have a diagnosis of ASD themselves (an elevated odds ratio of 30.38 compared to later born siblings of children without an ASD diagnosis). However, later born siblings of probands with ASD also had an elevated likelihood of an ADHD diagnosis (3.80%; odds ratio 3.7). Conversely, for later born siblings of probands with an ADHD diagnosis the within-condition recurrence rate for ADHD was 12.47% (odds ratio compared to later born

siblings of children without an ADHD diagnosis 13.05) and the cross-condition recurrence rate for ASD was 1.92% (odds ratio 4.35). This is likely if anything to be an underestimate, since children with a diagnosis of both ASD and ADHD were placed in the ASD group.

These within- and cross-condition recurrence figures are of important clinical utility in terms of informing discussions with parents about the need for enhanced developmental surveillance for neurodevelopmental conditions such as ASD and ADHD in their younger children. However, there are some limitations to the clinical utility of the data from this important study. The sample sizes are modest, comprising *n*=730 later born children with older probands with an ADHD diagnosis and *n*=158 later born children with older probands with an ASD diagnosis. As a result, the confidence intervals of the elevated odds ratios reported are relatively wide (see Table 2) and this imprecision should add caution to how this information is conveyed to parents; though it is clear that the later born siblings are at considerably elevated likelihood of themselves going on to have ASD and ADHD. Families with an older child who was typically developing but who subsequently had a child with ASD or ADHD and another younger child were removed from the control group, perhaps leading to slightly lower estimates of the likelihood of a subsequent diagnosis after a typically developing child. One useful re-analysis of large population and registry databases[4,5] – with larger population-representative samples – would be to separate out and report recurrence rates for later born siblings rather than all siblings (earlier and later born combined) in these studies and we encourage the authors of these studies to do this.

Another set of different clinical issues also arise from these considerations. One question pertains to when such information should be imparted to parents. Often, parents seeking a diagnosis have known for some time that something is different about their child, and the developmental and behavioural difficulties their children are experiencing motivate the clinical consultation. A diagnosis can help parents to recognise and understand some of the challenges their child is

experiencing and should provide a gateway to information and support services that can help families support their child and anticipate their needs. Proactive monitoring of younger children for signs of ASD and ADHD could remove significant sources of stress in the process of seeking a diagnosis. However, we suspect that there is wide variation in clinical practice in how information about the potential likelihood of another diagnosis in their younger child is presented. It may not be best to impart this information at the initial feedback from the diagnostic consultation itself but at a later review meeting when parents have had the opportunity to find out more about ASD or ADHD and adjust to their new understanding of their child and family. We expect that there is wide variance in how knowledgeable and confident clinicians feel about imparting information about the familial nature of neurodevelopmental conditions. Whilst studies such as the present one will help to provide accessible and clinically translatable estimates of recurrence, more specialist training or even specialist genetic counselling services might have to be developed to provide this information to families sensitively and clearly, in the way that is increasingly the case for more monogenic forms of neurodevelopmental conditions[7].

The increasing recognition of within-child and within-family co-occurrence of neurodevelopmental conditions such as ASD and ADHD has also spurred developmental studies that aim to help us understand common and distinct mechanisms that lead to such outcomes. Many studies over the past 15 years have prospectively studied infants with older siblings with ASD to identify the neural and developmental changes that fall on the causal path to later autism symptoms[8,9]. Findings suggest that whilst overt behavioural differences are not consistently found until the second year of life, various neurodevelopmental differences may be present as early as six months of age that presage later emergent symptoms and the eventual development of an ASD clinical profile[7,8]. Similar studies of infants at familial increased likelihood of developing ADHD have been far fewer, although several are now underway[6,10]. The present study suggests that the rates of an ADHD diagnosis in an infant with and older sibling with ADHD are similar to the rates of an ASD

diagnosis in an infant with an older sibling with ASD, making this design feasible. More recently, such studies have begun to incorporate the increasing recognition that infants with older siblings with ASD may also be more likely to develop other neurodevelopmental conditions. In other work, Miller, Iosif and colleagues[11] have shown not only (consistent with the current paper) that by mid-childhood rates of ADHD diagnosis are elevated in siblings with an older proband with ASD but also that in these individuals there is evidence of atypical visual attention from as early as the first six months of life. We have recently examined infant predictors of mid-childhood ASD and ADHD traits in our own prospective study of younger siblings with probands with ASD[12] and found that whilst increased activity levels of poor inhibitory control were associated with later ADHD traits they were not associated with later ASD traits, suggesting that early developmental pathways to ADHD might be distinct from ASD. A recent study by Constantino and colleagues[13] has found that at eighteen months of age traits of early ASD behaviours were both largely independent from those of early general psychopathology and that the former were highly heritable but the latter largely environmentally influenced. They suggest that the widely observed co-occurrence of such traits later in childhood might operate from interactions over time between these independent susceptibilities. Identification of the underlying mechanisms of co-occurrence between neurodevelopmental conditions such as ASD and ADHD is important not only to better understand aetiology but also to guide efforts towards targeted pre-emptive early intervention, examples of which have begun to emerge[14,15].

The current paper[1] should be read by both the clinical and the research readership of the journal. It utilises a simple and transparent design to report novel data on later born within- and cross-condition recurrence of ASD and ADHD in a way that is utilisable in the clinic but also motivates research to understand how and why these conditions so commonly co-occur both within individuals and within families. Future research should develop and test early, pre-emptive

interventions to ameliorate aspects of these neurodevelopmental conditions that can considerably challenge children and those who care for them.

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